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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,641	08/30/2001	Philip A. Beachy	JHUC-P01-017	9388

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/943,641	**Applicant(s)** BEACHY ET AL.	
	Examiner Gyan Chandra	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 October 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4,5,8-23 and 26-32*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet .
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER

Continuation of 3. NOTE: The claim amendments require additional searches, i.e., NPL.

Applicant's Response to Final Rejection filed on 10/30/2006 is acknowledged. The rejection of claims 1,4,5, 8, 19 -27, and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al, is maintained for reasons of record on p. 3-6 of Office Action mailed on 06/14/05.
Applicants argue that Sommers et al teach random and site directed mutageneis to substitute the amino terminus and transmembrane regions of the STE2 gene in yeast for studying the amino acids responsible for switching a receptor between active and inactive stages. Applicants argue that Sommers et al do not teach providing a library of coding sequences for activating mutations of candidate receptor or ion channel wherein amino acids are replaced for small or medium side chain amino acids for large chain amino acids while maintaining charge. Further, Applicants argue that Herrick-Davis et al teach site directed mutagenesis to substitute amino acids with different polarity or longer side chains. Applicants state that individual references do not provide motivation to combine them together.
Applicants' arguments have been fully considered but have not been found to be persuasive because (as stated in the previous Office Action) Sommers et al. teach a method for identifying constitutively activating mutations by making a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene (page 6899, left column, 2nd paragraph) in yeast and then screening for these mutations for the receptor activation. Sommers et al. teach that introduction of mutations in an a-factor receptor (a yeast G protein coupled receptor) to constitutively activate the receptor 2, 5, 7 or 20 fold. Further, Herrick-Davis et al teach application of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions.They teach substitution of amino acids to increase the binding affinity of 5HT to the mutant receptor (page 1140, left column, 3rd paragraph). Therefore, the person of ordinary skill in the art would have been motivated do so with a reasonable level of success to more efficiently study the effect of various mutations in side chain amino acids, within the residues of helical domain or the interfaces between transmembrane helices as taught by Sommers for constitutive activation of the receptor in order to increase the probability of finding novel therapeutic agents for an antagonist or inverse agonist as taught by Herrick-Davis et al. Applicants' arguments that the amino acid substitions are performed while maintaining the charge is not being addressed at present as it would require further searches.

The rejection of claims 9-18 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al. as applied to claims 1,4,5, 8, 19 -27, 29-32 above, and further in view of Barak et al, is maintained for the reasons of record on p. 6-7 of Office Action mailed on 06/14/2005.
Applicants argue that Barak et al teach using a heterologous reporter system for determining activity but Barak et al do not teach using a library of site directed mutations.
Applicants' arguments have been fully considered but they are not persuasive because the person of ordinary skill in the art would have been motivated to study the effect of various constitutive mutations for finding novel therapeutic agents for an antagonist or inverse agonist as taught by Herrick-Davis in a mammalian heterologous reporter system as Barak et al teach using GFP reporter system to measure the activation of a GPCR that can be used to study constitutive mutations.

The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al and Barak et al, as applied to claims 1, 4, 5, 8-27 and 29-32 above and further in view of Lerner et al, is maintained for the reasons of record on p. 7-9 of Office Action mailed on 06/14/05.
Applicants argue that Lerner et al disclose identifying antagonists or agonists for a G-protein coupled receptor using a pigment cell. However, they do not teach use of a library of site directed mutations generated by replacing coding sequences to study constitutive activation and that there is no motivation to combine set forth references.

Applicants' arguments have been fully considered but they are not persuasive because the person of ordinary skill in the art would have been motivated to study the effect of various constitutive mutations for finding novel therapeutic agents for an antagonist or inverse agonist as taught by Herrick-Davis in a mammalian pigment aggregation system as taught by Lerner et al by measuring activation of GPCR through changes in the level of cAMP in a frog melanophore assay.
In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection of claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al. in view of Dahiyat et al., is maintained for the reasons of record of Office Action mailed on 06/14/2005.
The rejection of claims 9, 11-18, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al in view of Dahiyat et al. as applied to claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 above and further in view of King et.al is maintained for reasons of record as Office Action mailed on 12/15/2004.
Applicants reiterate their arguments of 11/18/2005 (see Remarks, page 10-11) that King et al do not provide a library of coding sequences for potentially activating mutations. Applicants' arguments have been fully considered but they are not deemed persuasive because the combined teachings of Herrick-Davis et al and Dahiyat et al in further view of King et al teach the invention as being instantly claimed.
The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al. in view of Dahiyat et al. as applied to claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 above and further in view of Lerner et al, is maintained for the reasons of record in the previous Office Action.

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